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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/235,875	01/22/99	MADISON L	MBX020

EXAMINER	
NELSON, A	
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DATE MAILED: 10/11/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/235,875	Applicant(s) Lara Madison et al.
	Examiner Amy Nelson	Group Art Unit 1638

☒ Responsive to communication(s) filed on *Aug 28, 2000* .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-34* is/are pending in the application.

Of the above, claim(s) *28-30 and 34* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-27 and 31-33* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *12 & 13*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Election/Restriction

1. Applicant's election with traverse of Group V, Claims 1-8, 11-27, and 31-33, in Paper No. 11, filed 8/28/00, is acknowledged. The traversal is on the ground(s) that Claims 1-8, 11-27, and 31-33 are directed to a method of producing polyhydroxyalkanoates which comprise 3-hydroxyhexanoate by introducing a variety of different combinations of genes encoding enzymes in PHA biosynthetic pathway. Applicant also notes that Claims 9 and 10 have not been in included in any of the Groups, and that Group VII is understood to be directed to a transformation method with a crotanase gene.

Upon further consideration and thorough examination of the Specification, Examiner has determined that it would not be an undue burden to examine all of Groups I-VIII. Claims 9 and 10 were intended to be included in Group V. Therefore, Claims 1-27, and 31-33 will be examined.

2. Claims 28-30, and 34 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

3. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

4. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any

amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Drawings

5. The drawings filed 6/21/99 have been approved by the Draftsperson.

Claim Objections

6. Claims 2, 4, 5, 10, and 32 are objected to because of the following informalities:

At Claims 2, line 1, Claim 5, line 1, Claim 10, lines 1-2, and Claim 32 "a bacteria" should be --a bacterium--.

At Claim 4, line 2, "Brassica" should be italicized.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-27, and 31-33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claimed invention is drawn broadly toward a transgenic organism comprising at least one transgene encoding PHB polymerase, PHA polymerase, β-ketothiolase, β-ketoacyl-CoA reductase, D-specific enoyl-CoA hydratase, crotanase, butyryl-CoA dehydrogenase, and 3-hydroxybutyryl-CoA dehydrogenase. Applicant describes bacterial genes encoding each of PHB polymerase, PHA polymerase, β-ketothiolase, and β-ketoacyl-CoA reductase. Applicant teaches a single gene encoding each of crotanase, butyryl-CoA dehydrogenase, and 3-hydroxybutyryl-CoA dehydrogenase from *Clostridium acetobutylicum*. Applicant teaches a single gene encoding D-specific enoyl-CoA hydratase from *Aeromonas caviae*. Applicant does not describe the composition or structure of other genes encoding PHB polymerase, PHA polymerase, β-ketothiolase, β-ketoacyl-CoA reductase, D-specific enoyl-CoA hydratase, crotanase, butyryl-CoA dehydrogenase, and 3-hydroxybutyryl-CoA dehydrogenase, and hence it is not clear from the instant specification that the Applicant was in possession of the invention as broadly claimed.

See *University of California V. Eli Lilly and Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997), which teaches that the disclosure of a process for obtaining cDNA from a particular organism and the description of the encoded protein fail to provide an adequate written description of the actual cDNA from that organism which would encode the protein from that organism, despite the disclosure of a cDNA encoding that protein from another organism.

9. Claims 1-27, and 31-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification is enabling only for claims limited to transgenic bacteria comprising a bacterial gene

encoding β-ketoacyl-CoA reductase, a bacterial gene encoding β-ketothiolase, and an *A. caviae* gene encoding PHB polymerase that accepts 3-hydroxyhexanoyl CoA, and transgenic bacteria comprising a bacterial gene encoding PHB polymerase and an *A. caviae* gene encoding D-specific enoyl-CoA hydratase, as well as a method for producing polyhydroxyalkanoates comprising 3-hydroxyhexanoate by culturing said transgenic bacteria. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are indefinite for the reasons discussed below. However the claims appear to be broadly drawn to a transgenic organism comprising at least one transgene encoding PHB polymerase, PHA polymerase, β-ketothiolase, β-ketoacyl-CoA reductase, D-specific enoyl-CoA hydratase, crotanase, butyryl-CoA dehydrogenase, or 3-hydroxybutyryl-CoA dehydrogenase, as well as to methods of production of polyhydroxyalkanoates comprising 3-hydroxyhexanoate therewith.

Applicant teaches transformation of *E. coli* with a gene encoding PHB polymerase from *A. caviae* that accepts 3-hydroxyhexanoyl CoA, as well as with *R. Eutropha* genes encoding β-ketoacyl-CoA reductase and β-ketothiolase (phbAB genes) (Example 2). Applicant teaches that when the *E. coli* is grown in the presence of butyrate or butanol, poly (3-hydroxybutyrate-co-3-hydroxyhexanoate) (PHBH) copolymer is produced, which contains 3-hydroxyhexanoate (HH) comonomer (Examples 2 and 5). Applicant teaches isolation of a gene from *Z. ramigera* encoding

β-ketoacyl-CoA reductase, genes from *C. acetobutylicum* encoding crotanase, butyryl-CoA dehydrogenase, and 3-hydroxybutyryl-CoA dehydrogenase, and genes from *N. salmonicolor* encoding β-ketothiolase and PHB polymerase (Example 3). Applicant also teaches transformation of *E. coli* with a gene encoding PHB polymerase from *A. caviae* as well as with a gene encoding D-specific enoyl-CoA hydratase from *A. caviae* (Example 4). Applicant teaches that when the *E. coli* is grown in the presence of octanoate and oleate, poly (3-hydroxybutyrate-co-3-hydroxyhexanoate) (PHBH) copolymer is produced, which contains 3-hydroxyhexanoate (HH) comonomer (Example 4).

In re Wands, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988) lists eight considerations for determining whether or not undue experimentation would be necessary to practice an invention. These factors are: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples of the invention, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims.

The state of the art for isolation of cDNA or genomic clones with a defined functionality is highly unpredictable. Significant guidance is required with regard to hybridization/wash conditions and/or PCR conditions that will allow specific isolation of the target genes. Applicant has characterized and isolated a single gene encoding PHB polymerase from *A. caviae* that accepts 3-hydroxyhexanoyl CoA, and a single gene encoding D-specific enoyl-CoA hydratase from *A. caviae*, and single genes from *C. acetobutylicum* encoding crotanase, butyryl-CoA

dehydrogenase, and 3-hydroxybutyryl-CoA dehydrogenase. Applicant has provided no guidance with respect to what hybridization/wash conditions or what PCR reaction conditions would allow specific isolation of additional functionally related genes. In the absence of such guidance, undue trial and error experimentation would be required to screen through the vast number of cDNA and genomic clones from *A. caviae*, *C. acetobutylicum* or another organism, to identify those that are functionally related to the instantly disclosed genes and likewise encode PHB polymerase that accepts 3-hydroxyhexanoyl CoA, D-specific enoyl-CoA hydratase, crotanase, butyryl-CoA dehydrogenase, or 3-hydroxybutyryl-CoA dehydrogenase. Moreover, Applicant has not provided guidance for isolation of genes encoding PHB polymerase, PHA polymerase, β-ketothiolase, or β-ketoacyl-CoA reductase other than from bacteria. The instant claims to methods and to transgenic organisms should be limited in scope to the scope of genes which were available at the time of the invention or for which guidance is provided in the instant specification.

Manipulation of biochemical pathways, particularly in eukaryotes, by transgenic means is highly unpredictable and difficult, because control at key branch points is generally resistant to flux changes (Stephanopolous et al.; TIB Tech. 11: 392-396, 1993, Abstract, p. 396). In plants, the phenotype which results from insertion of genes encoding enzymes in biochemical pathways is often surpising and unpredictable, and many times the desired goals are impossible to achieve (De Luca; Ag. Biotech. News Info. 5: 225N-229N, 1993).

Applicant's exemplification of production of PHBH copolymer which contains 3-hydroxyhexanoate (HH) comonomer by transformation of *E. coli* with either (1) a gene encoding

PHB polymerase from *A. caviae* that accepts 3-hydroxyhexanoyl CoA along with *R. Eutropha* genes encoding β-ketoacyl-CoA reductase and β-ketothiolase, or (2) a gene encoding PHB polymerase from *A. caviae* along with a gene encoding D-specific enoyl-CoA hydratase from *A. caviae*, does not enable broad claims to methods of transformation of any organism with any combination of the claimed genes. It is the specific combination of genes which is critical to the production of the particular type of polyhydroxyalkanoate of particular composition. Moreover, Applicant has provided no enabling guidance for production of polyhydroxyalkanoates containing 3-hydroxyalkanoate by transformation with a gene encoding crotanase, butyryl-CoA dehydrogenase, and/or 3-hydroxybutyryl-CoA dehydrogenase.

Lastly, it is noted, whereas Applicant has provided guidance for production of polyhydroxyalkanoates containing 3-hydroxyalkanoate in *E. coli*, Applicant has provided no guidance for transgenic plants or other transgenic organisms. As discussed above, phenotype is highly unpredictable in transgenic plants, particularly when manipulating large biochemical pathways. Further, it is not clear that substrate availability and regulation of polyhydroxyalkanoate production is comparable between bacteria and plants. Therefore, in the absence of specific guidance with respect to plants or other organisms, the instant claims should be limited to transgenic bacteria, and methods of transforming bacteria with the exemplified genes.

When the *Wands* factors are weighed it is concluded that undue experimentation would be required to practice the invention throughout the full scope of the claims, and therefore the invention is not enabled.

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 1-27, and 31-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

At Claim 1, "synthesizing" is not a positive method step. Synthesis of the polyhydroxyalkanoate is a natural biological process occuring in the transgenic organism. It is recommended that the claim be rewritten with a method step directed to introducing the transgene(s), or culturing the transgenic organism.

At Claim 1, line 3, "polyhydroxyalkanoate" (singular) is inconsistent with "polyhydroxyalkanoates" (plural) at line 1.

At Claim 3, line 2, "plants" (plural) is inconsistent with "plant" (singular) at line 1.

Claims 6-27 are improperly dependent on Claim 1. Applicant should amend the claims to clearly indicate how the single method step of Claim 1 (synthesizing) is modified. If additional method steps are intended then the claim language --further comprising-- should be inserted followed by the additional method step(s).

At Claim 7, line 1, "the enzyme" lacks proper antecedent basis.

At Claim 7, line 1, the phrase "derived from" is indefinite. There are many different types of derivatives, and hence it is not clear how the enzyme is derived. It is recommended that the phrase be changed to --from--.

At Claims 8, 9, 11, 13-18, and 23, line 1, "the organisms" (plural) lacks proper antecedent basis.

At Claim 11, the phrase "genetically engineered using a butyrate fermentation pathway" is indefinite. It is unclear what exactly from the pathway is used for genetic engineering. Genetic engineering is done with genes, not with biosynthetic pathways. Clarification is required.

Claims 18-27 are improperly dependent on Claim 1. Claim 1 is directed to a method with transgenic organisms comprising genes encoding specified enzymes. None of the specified enzymes are "fatty acid biosynthetic enzymes" as recited in Claim 18 or part of a "fatty acid oxidation complex" as recited in Claim 23. Therefore, Claims 18-27 do not further limit the parent claim, and recite limitations which are not encompassed by the parent claim. Appropriate correction is required.

At Claim 22, line 1, the phrase "derived from" is indefinite. There are many different types of derivatives, and hence it is not clear how the enzyme is derived. It is recommended that the phrase be changed to --from--.

At Claim 23, the phrase "genetically engineered using a fatty acid oxidation complex" is indefinite. It is unclear what exactly from the oxidation complex is used for genetic engineering. Genetic engineering is done with genes, not with oxidation complexes. Clarification is required.

At Claim 25, line 1, the phrase "derived from" is indefinite. There are many different types of derivatives, and hence it is not clear how the enzyme is derived. It is recommended that the phrase be changed to --from--.

At Claim 26, line 1, "the enzymes for epimerization" lacks proper antecedent basis.

At Claim 26, line 2, the phrase "derived from" is indefinite. There are many different types of derivatives, and hence it is not clear how the enzyme is derived. It is recommended that the phrase be changed to --from--.

At Claim 31, line 1, "genetically engineered organism" should be changed to --transgenic organism-- to be consistent with Claim 1.

Claim Rejections - 35 USC § 101

12. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

13. Claim 31 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Specifically, the claim reads on a transgenic human which is non-statutory subject matter.

Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

15. Claims 1, 2, 5-11, 15, 31, and 32 are rejected under 35 U.S.C. 102(a) as being anticipated by Fukui *et al.* (J. Bacteriol. 179: 4821-4830, 1997).

Fukui discloses a method for producing polyhydroxyalkanoates containing 3-hydroxyhexanoate by transformation of *Alacaligenes eutrophus* and *Pseudomonas putida* with genes from *Aeromonas caviae* encoding PHA synthase (polymerase) and/or enoyl-CoA hydratase, as well as the transgenic bacteria thereby obtained (Abstract; p. 4822, Tables 2-4). Therefore, all of the claim limitations have been previously disclosed by Fukui.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy J. Nelson whose telephone number is (703) 306-3218. The examiner can normally be reached on Monday-Friday from 8:00 AM - 4:30 PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Paula Hutzell, can be reached at (703) 308-4310. The fax phone number for this Group is (703) 308-4242 or (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application, or if the examiner cannot be reached as indicated above, should be directed to the Group receptionist whose telephone number is (703) 308-1234.

Amy Nelson

AMY J. NELSON, PH.D
PRIMARY EXAMINER

Amy J. Nelson, Ph.D.
October 9, 2000